POSTER SESSION II

ALLOGENEIC TRANSPLANTS

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Factors Influencing Pulmonary Toxicity in the Setting of Total Body Irradiation-Based Myeloablative Conditioning in Children Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Mustafa Abugideiri [1], Ronica H. Nanda [2], Charlotte Butker [3], Sungjin Kim [4], Elizabeth Butker [2], Mohammad K. Khan [2], Natia Esiashvili [2]. [1] *The George Washington University School of Medicine and Health Sciences, Washington, DC;* [2] *Radiation Oncology, Emory University, Winship Cancer Institute, Atlanta, GA;* [3] *Emory University, Atlanta, GA;* [4] *Biostatistics, Emory University, Winship Cancer Institute, Atlanta, GA*

Purpose: To evaluate factors associated with increased risk of pulmonary toxicity in pediatric patients after myeloablative conditioning using total body irradiation (TBI) followed by allogeneic hematopoietic stem cell transplantation (HSCT).

Methods and materials: The records of 129 consecutive pediatric patients (range, 1-21 years) who underwent TBI-based myeloablative conditioning for hematologic malignancies at our institution between January 2003 and May 2014 were reviewed. Although total TBI dose ranged from 10.5 to 14Gy, lung doses were reduced to 10Gy with partial transmission blocks. The TBI dose rate ranged from 5.57cGy/min to 20.85cGy/min.

Results: Pulmonary toxicity developed in 70.5% of patients, which proved to be fatal in 38.5% of those patients. Patients with any type of infection at any point during the follow-up period were more likely to develop pulmonary toxicity (p=0.009), and patients with bacterial infection during the follow-up period had the highest incidence of pulmonary toxicity (p=0.038). The presence of any grade of acute graft-versus-host-disease (GVHD) was associated with an increased incidence of pulmonary toxicity (p=0.034), which developed in 94.4% of patients with grade III-IV GVHD (p=0.001). TBI dose rate was significantly related to the development of pulmonary toxicity (p=0.0495). Pulmonary toxicity was 3.51 times more likely to develop in patients receiving a TBI dose rate greater than 15cGy/min (p=0.017). Overall survival was significantly shorter in patients who developed pulmonary toxicity (p=0.0053).

Conclusions: A high incidence of pulmonary toxicity was noted in this large series of homogeneously treated pediatric patients undergoing TBI for allogeneic HSCT. The presence of high grade acute GVHD and infection were the most significant factors contributing to the development of pulmonary toxicity. TBI dose rate should be aimed to be kept below 15cGy/min to decrease the risk of pulmonary injury.

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Encouraging Outcomes of Haploidentical Hematopoietic Stem Cell Transplantation—Single Centre Experience from a Resource Poor Country

Rayaz Ahmed [1], Narendra Agrawal [2], Anshul Gupta [2], Jyotsna Kapoor [2], Dinesh Bhurani [1]. [1] *Department of Haematology, Rajiv Gandhi Cancer and Research Center, New Delhi, India;* [2] *Hematology, Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India*

High cost of matched unrelated donor stem cells limits its use in resource poor countries. Haploidentical donor is readily available for most of patients and at much lower cost, so can be feasible for poor patients. Here, we are reporting the outcome of 19 patients (16 male, 3 female), median age 37 years(15-63 yrs), who underwent Haplo HSCT using peripheral blood stem cells(n=16) and marrow (n=3) during October 2011 to September 2014 at Rajiv Gandhi Cancer Institute & Research Centre (India) using non-myeloablative (NMA) and reduced intensity conditioning regimen (RIC) for hematological disorders (AA=2,ALL=4,AML=5,NHL=1,HL=2, MM=1,CML=5) with post-transplant cyclophosphamide for GvHD prophylaxis. Fourteen patients were in remission at the time of transplant. Seven patients received RIC with BuFluCy(n=5) and BuFlu(n=2), 12 patients received NMA conditioning with FluCyATG(n=3) and FluCyTBI(n=9). Median CD34 cell dose was 5 X10^{6}cells/kg. Fifteen patients (79%) were engrafted, with a median time to neutrophil engraftment of 15 days (range, 9-22) and platelet engraftment of 14 days (range, 10-46). Nine patients had documented bacterial infection in first 100 days whereas none had documented fungal infection. Primary and secondary CMV reactivation occurred in 7 (36.8%) and 2 (10.5%) patients. The estimated day 100 and 1 year overall survival (OS) was 84.2±0.84% & 52.1±0.127 % respectively. The estimated 1 year event free survival (EFS) & non-relapse mortality (NRM) was 48.4±0.123% & 26.3%. Cumulative incidence of aGVHD (II-IV) and (III-IV) was 26.3% & 5.2% whereas cumulative incidence of chronic GVHD at 1 year & 2 year was 15.8% & 10.5% respectively. Graft rejection was seen in 6 patients (31.5%, 5 primary and 1 secondary). These results suggest that this approach is safe & effective, with rapid multilineage engraftment, low rates of both aGVHD & cGVHD and low NRM.

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Plasma IL-7 and IL-15 Levels Vary Greatly after Low-Intensity Conditioning and May be Associated with Clinical Outcome in Recipients of High-Dose Sirolimus GVHD Prophylaxis

Syed Abbas Ali [1], Seth M. Steinberg [2], Miriam Mossoba [3], Joseph Rimando [4], Scott Rowley [5], Michele L. Donato [5], Kevin Camphausen [6], George Sigal [7], Fran Hakim [8], Ronald Gress [9], David Halverson [10], Daniel Fowler [8]. [1] *Experimental Transplant and Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD;* [2] *Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Rockville, MD;* [3] *ETIB, NCI, Bethesda, MD;* [4] *Medical Research Scholars Program, National Institutes of Health, Bethesda, MD;* [5] *John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ;* [6] *Radiation Oncology Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD;* [7] *Meso Scale Diagnostics, Gaithersburg, MD;* [8] *Experimental Transplantation and Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD;* [9] [*] *Co-Senior Experimental Transplantation and Immunology Branch/NCI/NIH, Bethesda, MD;* [10] *Experimental Transplantation and Immunology Branch, NCI, Bethesda, MD*

In previous studies using a preparative regimen of fludarabine (Flu) plus high-dose cyclophosphamide (Cy; total dose, 4800 mg/m^2) and GVHD prophylaxis of cyclosporine plus methotrexate, it was determined that transplant recipients had quite variable plasma levels of the T cell

Table 1
Cytokine Levels and Clinical Outcome

		SD Cohort		HD Cohort
Clinical Intervention[1]				
Flu/Cy-1200mg/m^2; PBSCT; CSA; T-Rapa DLI		✓		✓
Sirolimus Trough Target (ng/ml; day -2 to day +14)		5-10		20-30
Clinical Outcome[2]		n = 46		n = 20
Donor T-Cell Chimerism	day +14	50.7 ± 3.9		57.5 ± 6.3
	day +28	75.1 ± 3.5		78.1 ± 5.5
Donor Myeloid Cell Chimerism	day +14	47.4 ± 4.5		49.1 ± 10.1
	day +28	79.1 ± 2.8		74.0 ± 6.6
Acute GVHD, Classical		39.5%[†]		52.6%[‡]
Cytokine Levels[3]		n = 43		n = 19
IL-7 (day 0; pg/ml)		15.8 (11.4 - 48.3)		16.4 (13.7 - 45.2)
IL-15 (day 0; pg/ml)		19.4 (18.9 – 45.0)		22.1 (21.1 - 66.8)
Cytokine Correlation[4]				
IL-7 vs. Donor T Cell Chimerism d +14 IL-7 vs. Donor T Cell Chimerism d +28		weak		r = 0.58, P = 0.014 r = 0.59, P = 0.011
IL-7 vs. Donor Myeloid Chimerism d +14 IL-7 vs. Donor Myeloid Chimerism d +28		weak		r = weak r = weak
IL-15 vs. Donor T Cell Chimerism d +14 IL-15 vs. Donor T Cell Chimerism d +28		weak		r = 0.68, P = 0.003 r = 0.47, P = 0.048
IL-15 vs. Donor Myeloid Chimerism d +14 IL-15 vs. Donor Myeloid Chimerism d +28		weak		r = 0.49, P = 0.048 r = 0.53, P = 0.025
IL-7 vs. Acute GVHD		P = 0.40		P = 0.012
IL-15 vs. Acute GVHD		P = 0.27		P = 0.024

[1] All patients received HLA-matched, T cell replete PBSCT for therapy of refractory hematologic malignancy after low-intensity Flu/Cy conditioning (total Cy dosing reduced from 4800 to 1200 mg/m^2). "SD", indicates standard-dose sirolimus cohort; "HD", indicates high-dose sirolimus cohort. All pts received pre-emptive DLI with rapamycin-resistant T cells (T-Rapa; administered at d14 post-SCT).

[2] Chimerism was determined by VNTR-PCR; acute GVHD incidence, grade II-IV through d100 post-SCT. Values shown for chimerism are means ± standard error of the mean (SEM). [†]27 patients with GVHD out of 62 evaluable patients; [‡]10 patients with GVHD out of 19 evaluable patients.

[3] Mean cytokine levels and range in pg/ml generated by multiplexed analysis (MesoScale Diagnostics, LLC).

[4] Spearman correlations were used to determine the association of IL-7 and IL-15 values with chimerism; correlations with r > 0.40 were considered to be at least moderately correlated and are therefore listed, along with a p-value for a test of r = 0; correlation values less than this were considered to be weak and were not provided. The Wilcoxon rank sum test was used to test IL-7 and IL-15 levels with acute GVHD or not.

homeostatic cytokines IL-7 (*Dean et al; JCO, 2008*) and IL-15 (*Boyiadzis et al; BBMT, 2008*) and cytokine levels were associated with acute GVHD (IL-7) or pattern of immune reconstitution (IL-15). However, it is not known whether recipients of lower-intensity conditioning or sirolimus-based GVHD prophylaxis have variable levels of these cytokines or whether such potential cytokine variability is associated with clinical outcome. To begin to address this, we measured multiple cytokine levels (MesoScale multiplex assay; current analysis restricted to IL-7 and IL-15 levels at day 0 of transplant) in recipients of low-intensity conditioning (Flu/Cy; total Cy dose, 1200 mg/m^2; see Table 1). Patients received GVHD prophylaxis consisting of cyclosporine plus short-course sirolimus (d2 through d14 post-SCT) at either standard-dose (n=46; "SD Cohort") or high-dose (n=20; "HD Cohort") (target trough level: 5-10 or 20-30 ng/ml, respectively). All patients received pre-emptive DLI consisting of rapamycin-resistant T cells (*Fowler et al; Blood, 2013*); however, in the current study, T cell manufacturing was reduced from 12 days to 6 days. Clinical outcomes (Table 1) were similar in SD and HD Cohorts, including: donor T cell and myeloid cell chimerism pre-DLI (d14 post-SCT) and post-DLI (d28 post-SCT), and incidence of classical acute GVHD. Remarkably, a wide range of IL-7 and IL-15 values were detected at day 0 of SCT in both SD and HD Cohorts (no difference between cohorts). In the SD Cohort, there was no association of IL-7 or IL-15 values with donor T cell chimerism, myeloid cell chimerism, or acute GVHD. However, in the HD Cohort, IL-7 values were associated with donor T cell chimerism and GVHD; and, IL-15 values were associated with donor T cell chimerism, myeloid cell chimerism, as well as GVHD. In conclusion, these data indicate that: (1) IL-7 and IL-15 values differ widely amongst recipients of low-intensity conditioning; and (2) IL-7 and IL-15 values were potentially associated with allo-engraftment and GVHD in the setting of high-dose sirolimus but not standard-dose sirolimus. This latter result provides a new insight into the pharmacodynamics of mTOR blockade post-transplant, and suggests that a more complete block of cytokine receptor signaling in vivo can unmask relationships between cytokine biology and post-transplant outcome.

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Immunogenetic Cross-Talk in Patients Transplanted for AML: CMV Reactivation Is Not a Strong Stimulus for Immune Response Against Leukemia

Apostolia Papalexandri, Ioanna Sakellari, Chrysa Apostolou, Zoi Boussiou, Damianos Sotiropoulos, Sofia Charalampidou, Panayiota Zerva, Tasoula Touloumenidou, Varnavas